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Thirty-day laboratory-based surveillance for carbapenem-resistant Enterobacteriaceae in the Minneapolis-St. Paul metropolitan area

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Abstract

Carbapenem-resistant Enterobacteriaceae (CRE) are a growing problem in the United States. We explored the feasibility of active laboratory-based surveillance of CRE in a metropolitan area not previously considered to be endemic for CRE. We provide a framework to address CRE surveillance and to monitor changes in CRE incidence over time.

In the United States, 43 states have confirmed detection of Enterobacteriaceae that produce the *Klebsiella pneumoniae* carbapenemase (KPC).[1] Other carbapenemases, including the New Delhi metallo-β-lactamase (NDM), have also been reported.[2] As carbapenemase-producing carbapenem-resistant Enterobacteriaceae (CRE) are not reportable in most jurisdictions, the true prevalence of these organisms in the United States is not known. Accurate surveillance data for CRE, particularly carbapenemase-producing CRE, are important and can provide situational awareness, improve understanding of CRE epidemiology, and contribute to CRE-specific infection prevention efforts.

The following describes efforts made by the Minnesota Department of Health (MDH), a participant in the Emerging Infections Program, funded and coordinated by the Centers for Disease Control and Prevention (CDC), to develop an ongoing active surveillance program of CRE in a metropolitan area not previously considered to be endemic for CRE.

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The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the CDC.

Fourteen laboratories, including three reference laboratories, were identified by hospitals, long-term acute care hospitals, long-term care facilities, and clinics in the two most populous counties in the Minneapolis-St. Paul metropolitan area (Hennepin and Ramsey County; population 1,661,065 in 2010). A telephone survey was conducted with the microbiology supervisor at each site with the purpose of understanding the method(s) used to detect carbapenem resistance and confirm carbapenemase production. We then used data gathered during the survey to design a 30-day pilot surveillance project.

Laboratories were asked to collect data on the number of unique Enterobacteriaceae isolates identified during a 30-day surveillance period. Isolates were from clinical cultures from all sites ordered independently by clinicians. No distinction was made with regard to infection or colonization.

Laboratories also submitted isolates that met the MDH CRE definition: nonsusceptible to imipenem (MIC ≥2 μg/ml), meropenem (MIC ≥2 μg/ml), or ertapenem (MIC ≥1 μg/ml).[3] Separate criteria were used for *Morganella*, *Proteus*, and *Providencia* spp. because of intrinsic mechanisms that increase the MIC of imipenem: resistant to imipenem (MIC ≥4 μg/ml) plus nonsusceptible to meropenem or ertapenem. All laboratories used automated testing instruments (ATI) to determine the MIC of antibiotics according to the manufacturer's specifications. Additional testing or interpretation (e.g. expert rules) beyond the results from the ATI was not considered in this project.

Total counts of Enterobacteriaceae and isolates meeting the CRE definition were submitted to the MDH Public Health Laboratory. Isolates were submitted with a submission form containing demographic data, culture site, facility where the specimen was collected, and susceptibility testing results. All submitted isolates underwent broth microdilution (BMD) susceptibility testing using GNX2F Sensititre plates (TREK Diagnostic Systems, Cleveland, OH) and polymerase chain reaction (PCR) testing for bla_{KPC} and bla_{NDM}.[4]

Institutional review board evaluation was not required due to the Minnesota State Communicable Disease Rule regarding reporting of CRE cases. In addition, the project was reviewed at CDC and was determined to be "non-research."

Twelve of 14 laboratories (10 clinical, two reference) participated in the survey. Seven laboratories used the modified Hodge test to confirm carbapenemase production. No laboratories performed PCR for carbapenemase genes.

Twelve of 14 laboratories (11 clinical, one reference) participated in the 30-day pilot surveillance. Laboratories reported 7,534 unique Enterobacteriaceae during the 30-day period. Sixty (0.8%) isolates met our CRE definition for submission. Demographic data, location, and culture site of the submitted isolates are shown in Table 1. Of the 60 isolates, 16 (27%) were also resistant to all third-generation cephalosporins (3GC).

Eight (13%) of 60 isolates were nonsusceptible to at least one carbapenem by BMD testing (3 *E. cloacae*, 1 *E. coli*, and 4 *K. pneumoniae*), and 52 were susceptible to all carbapenems. Five of the eight isolates (1 *E. cloacae*, 1 *E. coli*, and 3 *K. pneumoniae*), were also resistant to all 3GC tested (cefotaxime and ceftazidime). One hundred twenty individual

susceptibility tests (i.e., 120 combinations of 60 isolates tested against ≥1 carbapenem) by ATI were compared with matched BMD test results. Major errors, defined as resistant by ATI and susceptible by BMD, are shown in Table 2; the proportion of major errors (i.e., carbapenem-resistant by ATI) was 74%.

PCR was performed on all isolates at the MDH Public Health Laboratory. Three of eight isolates nonsusceptible to a carbapenem by BMD testing were carriers of the bla_{KPC} gene (all *K. pneumoniae*). These three isolates tested resistant to each of the carbapenems tested by ATI and all 3GC by both methods. All other isolates were negative for bla_{KPC} and bla_{NDM} genes.

We report on a pilot surveillance project conducted by MDH to determine the feasibility of ongoing active laboratory-based surveillance of CRE in the two most populous counties in Minnesota. Based on our CRE definition, we found a low incidence of CRE in our catchment area (0.8%). Among those submitted only three were bla_{KPC} positive. Of the 60 isolates that met our CRE definition by ATI, only eight met this definition by BMD testing.

The discordant results between ATI and BMD testing results raise questions about the reproducibility of carbapenem susceptibility results. Our data suggest that the incidence of major errors depend on the carbapenem or device used during susceptibility testing. Our pilot was not designed to measure the efficacy of susceptibility testing, and therefore we cannot make any determination with regard to these methodologies, however further investigation is warranted. Of note, carriers of bla_{KPC} had high carbapenem MIC values and met our CRE definition regardless of the testing method.

We found that resistance to 3GC served as an additional selection criterion for identifying carbapenemase producers in lieu of other confirmatory tests. Adding 3GC resistance to our CRE definition would narrow the submitted isolates to 16, without eliminating the three bla_{KPC} producers. Additional selection criteria, such as 3GC resistance, may add specificity for carbapenemase-producers and be beneficial in areas with low incidence of carbapenemase-producing CRE.

The time needed for laboratories to collect accurate Enterobacteriaceae counts was an issue that was identified during our surveillance pilot. Some laboratories had automated means of de-duplicating data. For laboratories without this option, the time required to collect total, de-duplicated counts was prohibitive to participation.

One limitation of the pilot was the lack of participation from two reference laboratories during the 30-day surveillance pilot. Limitations in time and resources may have contributed to this, as participation was largely voluntary. Whether their participation would have had a significant impact on the proportion of CRE identified is unknown; however, inclusion of reference laboratories should be a goal of future surveillance efforts. Another limitation of the pilot was PCR testing for only the bla_{KPC} and bla_{NDM} genes as these are the most common carbapenemases in the United States. Future surveillance could include testing for other known carbapenemases.

These data provide new information regarding the presence of CRE in Minnesota, an area not considered to be endemic for CRE. The current pilot serves as a framework to address CRE surveillance and to monitor changes in the proportion and incidence of CRE over time. A more complete understanding of the limitations of detecting carbapenem resistance using ATI is needed as are phenotypic definitions that differentiate carbapenemase-producing CRE from non- carbapenemase-producing CRE. With this knowledge we can apply a functional CRE definition that allows for the tracking of carbapenemase-producing CRE.

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Table 1

Summary of characteristics from patients of submitted isolates, Hennepin and Ramsey Counties, Minnesota

	Total (n=60)
Demographics	
Male	18 (30%)
Median age in years (range)	70 (0–93)
Location at the time of culture	
Hospital	25 (42%)
Outpatient	22 (37%)
LTACH	3 (5%)
LTCF	10 (17%)
Culture site	
Urine	44 (73%)
Blood	4 (7%)
Sputum	10 (17%)
Surgical wound	2 (3%)

Note. LTACH, long-term acute care hospital; LTCF, long-term care facility.

Table 2

Major errors[a] detected between automated testing and BMD testing by carbapenem and by ATI

	Total	Carbapenem			ATI[b]		
		Imipenem	Meropenem	Ertapenem	Phoenix	Vitek Legacy	Vitek 2
Number of individual susceptibility tests with both ATI and BMD results	120[c]	58	11	51	40	2	78
Number resistant by ATI	27	7	2	18	15	2	10
Major errors (percentage)[d]	20 (74%)	6 (86%)	0 (0%)	14 (78%)	12 (80%)	0 (0%)	8 (80%)

Note. BMD, broth microdilution; ATI, automated testing instrument

[a] Major error occurs when an isolate is resistant by ATI and susceptible by BMD

[b] Phoenix, Becton Dickinson Diagnostic Systems, Sparks, MD; Vitek, bioMérieux, Durham, NC

[c] 120 is the number of individual susceptibility tests (isolate/antibiotic combinations) by ATI with a matched BMD test result

[d] Percentage of major errors is the number of major errors divided by the total number of resistant isolates by ATI